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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/077,572	10/13/1998	MICHAEL A. APICELLA	875001US2	6184

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EXAMINER
DEVI, SARVAMANGALA J N

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 04/03/2003

39

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/077,572	Apicella et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 29, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *22-26, 29, and 32-34* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *22-26, 29, and 32-34* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *32.*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Request for Continued Examination

1) A request for continued examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 01/29/03 (paper no. 37) has been entered.

Applicants' Amendment

2) Acknowledgment is made of Applicant's amendment filed 01/29/03 (paper no. 38) in response to the final Office Action mailed 02/21/01 (paper no. 27). With this, Applicants have amended the specification.

Status of Claims

3) Claims 22 and 29 have been amended via the amendment filed 01/29/03.

New claim 34 has been added via the amendment filed 01/29/03.

Claims 22-26, 29 and 32-34 pending and are under examination.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Information Disclosure Statement

6) Acknowledgment is made of Applicants' information disclosure statement filed 03/02/01 (paper no. 32). The information referred to therein has been considered and an initialed copy is attached to this Office Action (paper no. 39).

Objection(s) Maintained

7) The objection to the drawings made in paragraph 6 of the Office Action mailed 04/28/99 (paper no. 11) under 37 CFR 1.84 because of the reasons set forth by the Draftsperson is maintained

for reasons set forth therein. Correction is required. Applicants are asked to note the changes effected 03 May 2001, particularly the changes to the 'Timing of Corrections':

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 CFR 1.85; 1097 O.G. 36

New formal drawings must be filed with the changes incorporated therein. The art unit number, application number (including series code) and number of drawing sheets should be written on the reverse side of the drawings. Applicant may delay filing of the new drawings until receipt of the "Notice of Allowability" (PTOL-37 or PTO-37). If delayed, the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability" to avoid extension of time fees. Extensions of time may be obtained under the provisions of 37 C.F.R 1.136(a) for filing the corrected drawings (but not for payment of the issue fee). The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the three month shortened statutory period set in the "Notice of Allowability" (PTO-37). Within that three month period, two weeks should be allowed for review of the new drawings by the Office. If a correction is determined to be unacceptable by the Office, Applicant must arrange to have an acceptable correction re-submitted within the original three month period to avoid the necessity of obtaining an extension of time with extension fees. Therefore, applicant should file corrected drawings as soon as possible. Failure to take corrective action within the set

(or extended) period will result in ABANDONMENT of the application.

Abstract

8) This application currently does not contain an abstract of the disclosure as required by 37 C.F.R 1.72(b). However, as this application is filed under 371 with priority to PCT/US96/18984, a copy of the published abstract from PCT/US96/18984 (WO 97/19688) is placed in the instant application as page number 70. If Applicants desired changes to the abstract, such changes should be directed to the abstract of the PCT/US96/18984.

Sequence Non-compliance

9) The instant application contains a Sequence Listing as a part of the specification on page 60-63, which refers to specific SEQ ID numbers in the text. However, the application is not in sequence compliance as required under 37 C.F.R 1.821 through 1.825. It does not appear that a CRF and/or a paper copy of the Sequence Listing were filed in the case. Any sequences recited in the instant specification which are encompassed by the definitions for nucleotide and/or amino acid sequences as set forth in 37 C.F.R. 1.821(a)(1) and (a)(2) must comply with the requirements of 37 C.F.R 1.821 through 1.825. Note that branched sequences are specifically excluded from this definition.

APPLICANT MUST COMPLY WITH THE SEQUENCE RULES WITHIN THE SAME TIME PERIOD AS IS GIVEN FOR RESPONSE TO THIS ACTION, 37 C.F.R 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R 1.821(g).

Rejection(s) Withdrawn

10) The rejection of claims 22-26, 29, 32 and 33 made in paragraph 11 of the Office Action mailed 02/21/01 (paper no. 27) under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is withdrawn in light of Applicants' amendments to the claims and/or the base claim(s).

Rejection(s) Maintained

11) The rejection of claims 22, 23, 25 and 29 made in paragraph 9 of the Office Action mailed 04/28/99 (paper no. 11) and the rejection of claim 32 made in paragraph 23 of the Office Action mailed 10/11/00 (paper no. 25) under the judicially created provisional obviousness type double patenting over the cited claim(s) of application SN 09/565,943 is maintained for reasons set forth therein. Applicants have previously stated that they would consider filing a terminal disclaimer upon

notification of allowable subject matter.

The newly added dependent claim 34 is now included in this rejection

12) The rejection of claims 22-26, 29, 32 and 33 made in paragraph 10 of the Office Action mailed 04/28/99 (paper no. 11), paragraph 24 of the Office Action mailed 10/11/00 (paper no. 25) and maintained in paragraphs 6 and 8 of the Office Action mailed 02/21/01 (paper no. 27) under 35 U.S.C. § 112, first paragraph, with regard to the deposit of mutant bacteria, is maintained.

The new dependent claim 34 is now included in this rejection.

It is noted that Applicants amended the specification to provide information with regard to the deposit. It is further noted that Applicants have submitted a Declaration showing that two specific *htrB* mutant strains, 2019 B28 and 2019 B29, of non-typeable *Haemophilus influenzae* have been deposited. However, these strains do not appear to fall within the scope of the claims, as amended currently, because at least one these *htrB* mutants, B29, produces an endotoxin which shows two clearly discernible differences in the PEA and hexose contents as described in the paragraph bridging pages 16 and 17 of the specification. Therefore, the endotoxin of these mutants does not appear to be the same as the wild type endotoxin except for lacking at least one secondary acyl chain on lipid A, as recited currently. Furthermore, the scope of the claims broadly encompasses *htrB* mutants of any Gram negative bacterial pathogens, including any species of *Pseudomonas*, *Campylobacter*, *Moraxella*, *Neisseria* and *Haemophilus*, all allegedly capable of producing a mutant endotoxin of substantially reduced toxicity compared to the endotoxin of a wild-type bacterial pathogen of the same species as the mutant pathogen wherein 'the mutant endotoxin is the same as wild type endotoxin except for lacking at least one secondary acyl chain on lipid A'. As set forth previously, the various *htrB* mutant Gram-negative bacterial pathogens recited in the claims are required to practice the claimed method of making and using the mutant endotoxin product of the instant invention, as recited. As required elements, the mutant bacterial pathogens must be known and readily available to the public, or obtainable by a reproducible method set forth in the specification. It does not appear that the recited mutant bacteria are publicly available, or can be reproducibly isolated from nature without undue experimentation. Furthermore, except for the two specific *htrB* mutant strains, 2019 B28 and 2019 B29, of non-typeable *Haemophilus influenzae*, the specification appears to lack complete deposit information for the rest of the *htrB* Gram-negative

mutant bacterial pathogens that are specifically recited in the instant claims. Without a publicly available deposit of the recited bacterial mutants, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. The rejection stands.

Rejection(s) under 35 U.S.C § 112, First Paragraph (New Matter)

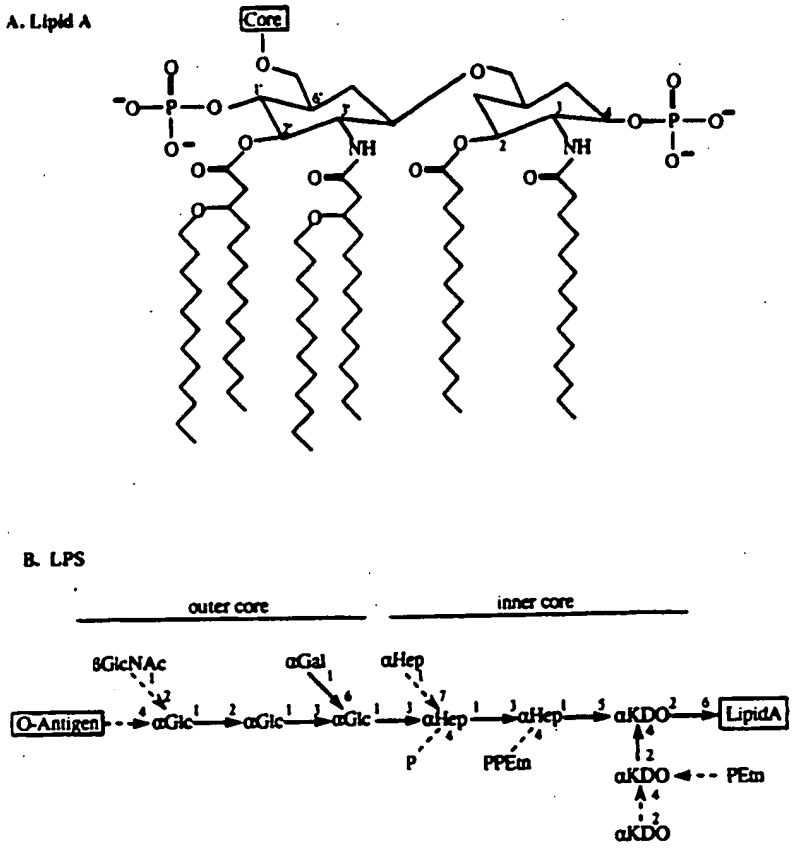
13) Claims 22-26, 29 and 32-34 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Independent claims 22 and 29, as amended, now include the limitation: "wherein the mutant endotoxin is the same as wild type endotoxin except for lacking at least one secondary acyl chain on lipid A". Applicants point to Figure 1, and Figures 2A and 2B, and state that 'Figure 1 depicts a wild type endotoxin (hexaacyl), and Figures 2A and 2B depict mutant endotoxins of the invention (pentaacyl and tetraacyl, respectively)'. Applicants also point to page 4 of the specification apparently describing Brief Description of the Figures and state that the only changes between Figure 1 and Figures 2A/2B is a decrease in the number of secondary acyl chains. Applicants also point to page 4, lines 3-9; page 7, lines 7-10; and page 13, lines 1-5 of the specification. Applicants cite case law and opine that adequate description under the first paragraph of 35 U.S.C. § 112, first paragraph, does not require literal support for the claimed invention. Applicants submit that one with ordinary skill in the art upon reading the full specification would understand that the claimed mutant endotoxin is the same as wild type endotoxin except for lacking one or more secondary acyl chains of lipid A.

However, a review of the specification indicates that the specification, as originally filed, does not provide descriptive support for the recitation: "wherein the mutant endotoxin is the same as wild type endotoxin except for lacking at least one secondary acyl chain on lipid A". Page 4 does not provide 'Brief Description of the Figures, and page 4, lines 3-9; page 7, lines 7-10; and page 13, lines 1-5 of the specification do not provide description as stated by Applicants in the paragraph bridging pages 3 and 4 of the amendment filed 01/29/03. Contrary to Applicants' assertion, Figure 1, and Figures 2A and 2B are limited to a diagrammatic representation of lipid A of a Gram negative bacterium, before and after *htrb* mutation respectively. The 'Brief Description of the Figures' on

page 5 of the specification for Figures 1, 2A and 2B describes 'a schematic representation of the general structure of lipid A' from a Gram negative enterobacterium and the LOS of an *htrB* mutant bacterium, as opposed to the general structure of an 'endotoxin'. The art does not recognize 'lipid A' depicted in these Figures to be the same as 'endotoxin'. For example, page 29 of the Karow dissertation (*Molecular Genetics of the Escherichia coli htrB gene*. Ph.D. Dissertation, The University of Utah, 1992, already of record), reproduced herebelow, clearly demonstrates that what is depicted in instant Figure 1 is the structural illustration of just the lipid A portion of endotoxin (see panel A) as opposed to the diagrammatic representation of the full endotoxin molecule which is shown therebelow in panel B.

29



Therefore, contrary to Applicants' assertion, one with ordinary skill in the art upon reading the full specification would not recognize that the claimed mutant 'endotoxin' is the same as 'wild type endotoxin' except for lacking one or more secondary acyl chains of lipid A. Both literal and non-literal descriptive support within the specification is contrary to what is being claimed.

Claim 22 also includes the new limitation: *htrB* 'gene encoding a wild type endotoxin' (see line 2). However, there is no descriptive support within the specification for a '*htrB* gene' that alone is capable of encoding a wild type endotoxin molecule.

Therefore, the above-identified new limitations in claims 22 and/or 29 are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitation(s), or to remove the new matter from the claim(s).

Rejection(s) under 35 U.S.C § 112, First Paragraph (Written Description)

14) Claims 22-26, 29 and 32-34 are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Instant claims claim a method of making a mutant endotoxin, the mutant endotoxin made and a method of producing antisera thereto wherein the endotoxin is "the same as wild type endotoxin except for lacking at least one secondary acyl chain on lipid A". However, there is no written description within the instant invention teaching such a method or the product. For example, the description in the paragraph bridging pages 16 and 17 indicate that the LOS obtained from a *htrB* mutant Gram negative bacterium, B29, is **not** the same the wild type LOS except for the lack of one or two secondary acyl chains, but instead, indicates that *htrB* LOS differs from the wild type LOS at least in its PEA and hexose contents in the inner core portion of the LOS. Figures 1, 2A and 2B do not and cannot show these changes because these Figures do not depict the inner core portion of the endotoxin, but only depict 'a schematic representation of the general structure of lipid A' from a

Gram negative enterobacterium and an *htrB* mutant bacterium. Contrary to Applicants' assertion, one with ordinary skill in the art upon reading the full specification would not recognize that the claimed mutant 'endotoxin' is the same as 'wild type endotoxin' except for lacking one or more secondary acyl chains of lipid A, as recited currently. Thus, there is lack of relevant identifying characteristics to permit one skilled in the art to predictably obtain the claimed product, *htrB* bacterial pathogen or its endotoxin having the properties as recited, absent adequate written description and guidance. That the written description provided within the instant specification is contrary to what is being claimed is also evident from paragraph 6 of the Gibson-Apicella Declaration filed along with Applicants' amendment filed 07/12/00 (paper no. 19), which paragraph is reproduced herebelow:

> 6. In addition, some **changes** in the phosphorylation pattern in the LOS and lipid A moiety are observed between wild type and *htrB*-mutant in *N. gonorrhoeae* strain 1291. These **changes** involve an increased level of phosphoethanolamine (PEA) in both the lipid A moiety as well as the oligosaccharide. [Emphasis added].

Clearly, one skilled in the art would not make out from the instant disclosure that Applicants were in possession of the claimed bacterial endotoxin product and methods of making the same or antisera thereto in view of the level of skill, knowledge in the art and Applicants' own description or statements. See Written Description Requirement, *Federal Register*, vol. 66, no. 4, Notices, pp. 1099-1111, 05 January 2001).

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

15) Claims 22-26, 29 and 32-34 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 29 is vague and confusing because the claimed method is for producing 'endotoxin-specific antisera', but the product being used to immunize an individual is an *htrB* mutant bacterial mutant or an endotoxin obtained from such a mutant (i.e., *htrB* endotoxin). Is the antisera produced specific to wild-type endotoxin or *htrb* endotoxin?

(b) Claim 22 is vague, indefinite and confusing in the recitation "method of making a mutant endotoxin comprising mutating an *htrB* gene encoding a wild type endotoxin in a wild type gram negative bacterial pathogen to provide the mutant endotoxin", because it is unclear how

mutating a *htrB* gene in a bacterium would 'provide' a mutant endotoxin' as opposed to a *htrB* mutant bacterium.

(c) Claim 29 is confusing. The claim is drawn to a method of producing 'endotoxin-specific antisera'. However, what is being collected in step be is "antibody produced from the immunized animal". An individual immunized, for example, with a *htrB* bacterial mutant would likely induce antibodies to different antigens present on the bacterial mutant, including non-endotoxin-specific antibodies. What is the specificity of the antibody collected in step b) of the claim? The scope of the claim is indeterminate.

(d) In dependent claims 23 and 25, for proper antecedence, it is suggested that Applicants replace the recitation "A mutant endotoxin made according to the method of claim 22" with --The mutant endotoxin made according to the method of claim 22--.

(e) Claims 24, 26 and 32-34, which depend directly or indirectly, from claim 22 or claim 29 are also rejected as being indefinite because of the vagueness or indefiniteness identified above in the base claim.

Remarks

16) Claims 22-26, 29 and 32-34 stand rejected.

17) Papers related to this application may be submitted to Group 1600, AU 1641 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

18) Any inquiry concerning this communication or earlier communication(s) from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail service. The Examiner can normally be reached on Monday to Friday from 7.15 a.m to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

S. DEVI, PH.D.
PRIMARY EXAMINER

April, 2003